FDA Workshop on FVIII Inhibitors

Bruce M. Ewenstein, MD, PhD
Global Medical Director, Hemophilia

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Product Descriptions

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RECOMBINATE and ADVATE Process Comparison

Host Cell	CHO	CHO
Transfection Vector	Human FVIII and vWF cDNAs	Human FVIII and vWF cDNAs
Cell Culture Medium	Bovine albumin, insulin, aprotinin	No human or animal plasma proteins
Cell Culture Process	Batch re-feed	Continuous ("chemostat") perfusion
Formulation	Human albumin	Mannitol, trehalose

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ADVATE and RECOMBINATE

- Full length FVIII molecules
- Comparable post-translational modifications
  - N- and O-linked glycosylation
  - Sialic acid
  - Tyrosine sulfation
- Specific activity
  - RECOMBINATE: >4000 IU/mg protein (prior to addition of albumin)
  - ADVATE: 4000-10000 IU/mg protein

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Clinical Evaluations

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ADVATE Immunogenicity Evaluation Pivotal Study

- Eligibility: > 150 ED for all other FVIII products
- Exclusion: history of inhibitor > 1.0 BU
- Inhibitor testing:
  - At study initiation
  - Prior to PK evaluations
  - After 15, 30, 45, 60 and 75 ED during prophylaxis treatment
  - At study termination

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ADVATE Clinical Studies
Inhibitor Assays

Theoretical limit of sensitivity	0.4 inh unit/mL	0 inh unit/mL
Values regarded as negative	<0.6 inh unit/mL	<0.4 inh unit/mL
Precision across a range of 11-117 inh units/mL	6.5-11.9% CV	4.6-5.7% CV

Semin Thromb Hemost 2000;26:195-203.

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ADVATE Pivotal Study Definition of Inhibitor

- High responder inhibitor
  - Inhibitor titer > 5 BU
  - Confirmed upon repeat testing in central laboratory
- Low responder inhibitor
  - Inhibitor titer 1 – 5 BU
- Transient inhibitor
  - Inhibitor titer ≤ 5 BU
  - No longer detectable at study termination
  - FVIII recovery ≥ 1.5 IU/ml per IU/kg
- If inhibitor titer ≤ 1 BU, plasma samples re-tested using the Nijmegen assay
- Later studies used only Nijmegen method

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ADVATE Pivotal Study
A Priori "Stopping Rule"

- Suspension of study
  - Occurrence of > 1 high titer inhibitor
  - Occurrence of > 2 low titer inhibitors
- DSBM evaluation

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Results from ADVATE Clinical Trials

Pivotal Study (n=108)

- Only 1 subject tested positive
  - Low titer inhibitor (2.0 BU) following 26 ED
  - No symptomatic evidence of inhibitor
  - Patient withdrew from study due to noncompliance
  - 8 weeks later, inhibitor undetectable, PK normal

Surgery (n=44), Pediatric PTP* (n=53), Continuation Studies (n=82)

- No inhibitor detected as of the latest interim study reports

*Eligibility: >50 ED

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RECOMBINATE Immunogenicity

PTP

- No (0/69) PTP developed a *de novo* inhibitor
  - One subject with a history of an inhibitor had a transient low titer inhibitor (0.8 BU) with decreased recovery and normal half-life

PUP

- Inhibitor testing occurred every 3 months
- 22 of 73 (30.1%) PUP developed an inhibitor
  - 7 high responders (> 10 BU)
  - 15 low responders (≤ 10 BU)
  - 5 transient inhibitors (max titers: 0.6 – 3 BU)
- Median exposure at inhibitor detection was 10 days

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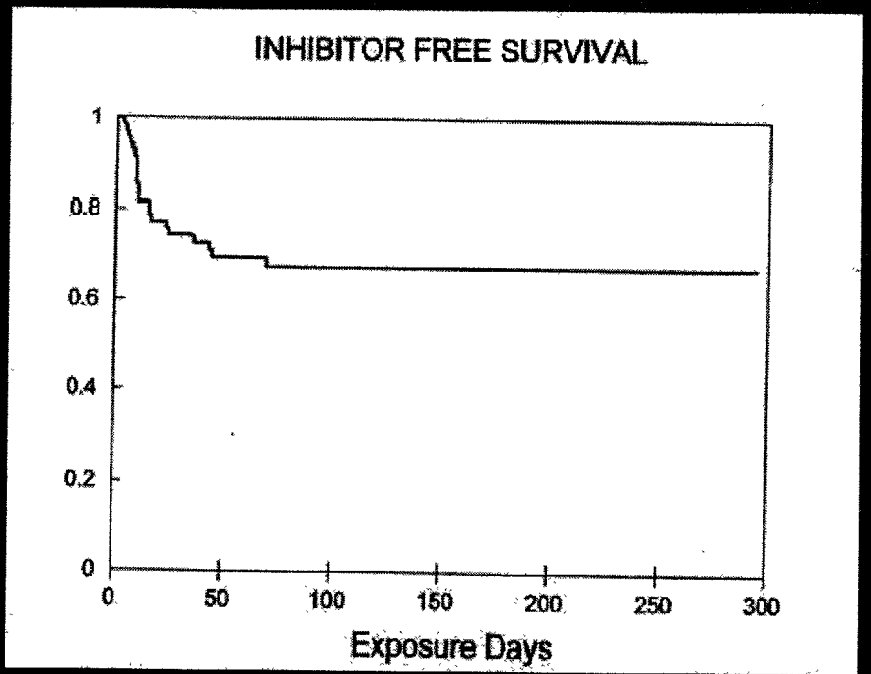
Time Course of Inhibitor Development RECOMBINATE PUP Study

- Probabilities of developing an inhibitor at 10, 20, and 40 days of RECOMBINATE exposure were 0.13, 0.24, 0.30, respectively



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Post-licensure Surveillance: RECOMBINATE

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Surveillance of Inhibitor Development from 1993 to 2002

- 89 documented inhibitor cases were prospectively collected during the 10 year post-licensure period
- Total distribution of 6.48 x 10^9 IU of RECOMBINATE and BIOCLATE
- Inhibitor incidence
  - Events per 10^6 IU distributed
  - Percent of treated patients based on estimation of individual exposure to RECOMBINATE / BIOCLATE
- Study results submitted for publication to *Haemophilia*

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Calculations and Assessments (1)

- Patients classified according to extent of prior FVIII therapy: 1-50, 50-150, or >150 ED
  - Based on reported ED or approximated from available clinical information
- Estimation of PUP (1-50 ED) and PTP (> 50 ED) in hemophilia A population
  - Prevalence (10.5 per 100,000 males)*
  - Incidence (1:6,410 live male births)*
  - 2.6% PUP and 97.4% PTP

*CDC Data

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Calculations and Assessments (2)

- Mean annual consumption of RECOMBINATE/ patient
  - Based on international multicenter prospective clinical trials
  - PUP (n=3), 48.6 x 10^3 IU
  - PTP (n=4), 148 x 10^3 IU
- Incidence rates of all inhibitors and high titer inhibitors were calculated separately
  - Predictors of inhibitor development were evaluated by multivariate Poisson modeling

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Patient Characteristics

Characteristic		n*	%
Age (y)	< 2	44	50.0
	2-6	18	20.4
	> 6	26	29.6
FVIII deficiency	Mild	7	9.6
	Moderate	8	11.0
	Severe	58	79.4
FVIII exposure (days)	1 - 50	60	78.9
	51 - 150	3	4.0
	> 150	13	17.1
Inhibitor titer (BU)	< 1	13	15.5
	1 - 5	27	32.1
	> 5	44	52.4

* Data not available for all patients

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Total and High Titer Inhibitor Incidence* Over a 10-year Period

	Incidence of inhibitors (%)			
	All	*(CI)*	>5 BU	*(CI)*
Total	0.317	(0.149-0.677)	0.158	(0.086-0.286)

- No lot-related clusters

* As percent of treated patients

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Inhibitor Incidence* by FVIII Exposure

	Incidence of inhibitors (%)			
FVIII EDs	All	*(CI)*	>5 BU	*(CI)*
1-50	11.9	(5.05-28.0)	5.96	(3.00-11.8)
>50	0.123	(0.030-0.512)	0.0554	(0.0113-0.271)

* As percent of treated patients

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Summary

- RECOMBINATE immunogenicity is low
- Immunogenicity data from RECOMBINATE clinical trials accurately predicted post-licensure surveillance results
- Data from ADVATE clinical trials (n=1 inh) and initial post-market surveillance (n=0 inh) are comparable to those of RECOMBINATE

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Future Perspectives

- Animal models are being refined for immunogenicity assessment of modified/non-native FVIII therapeutics
- Development of non-native FVIII molecules will require suitable novel methods of pre-clinical immunogenicity evaluation

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Back Up Slides

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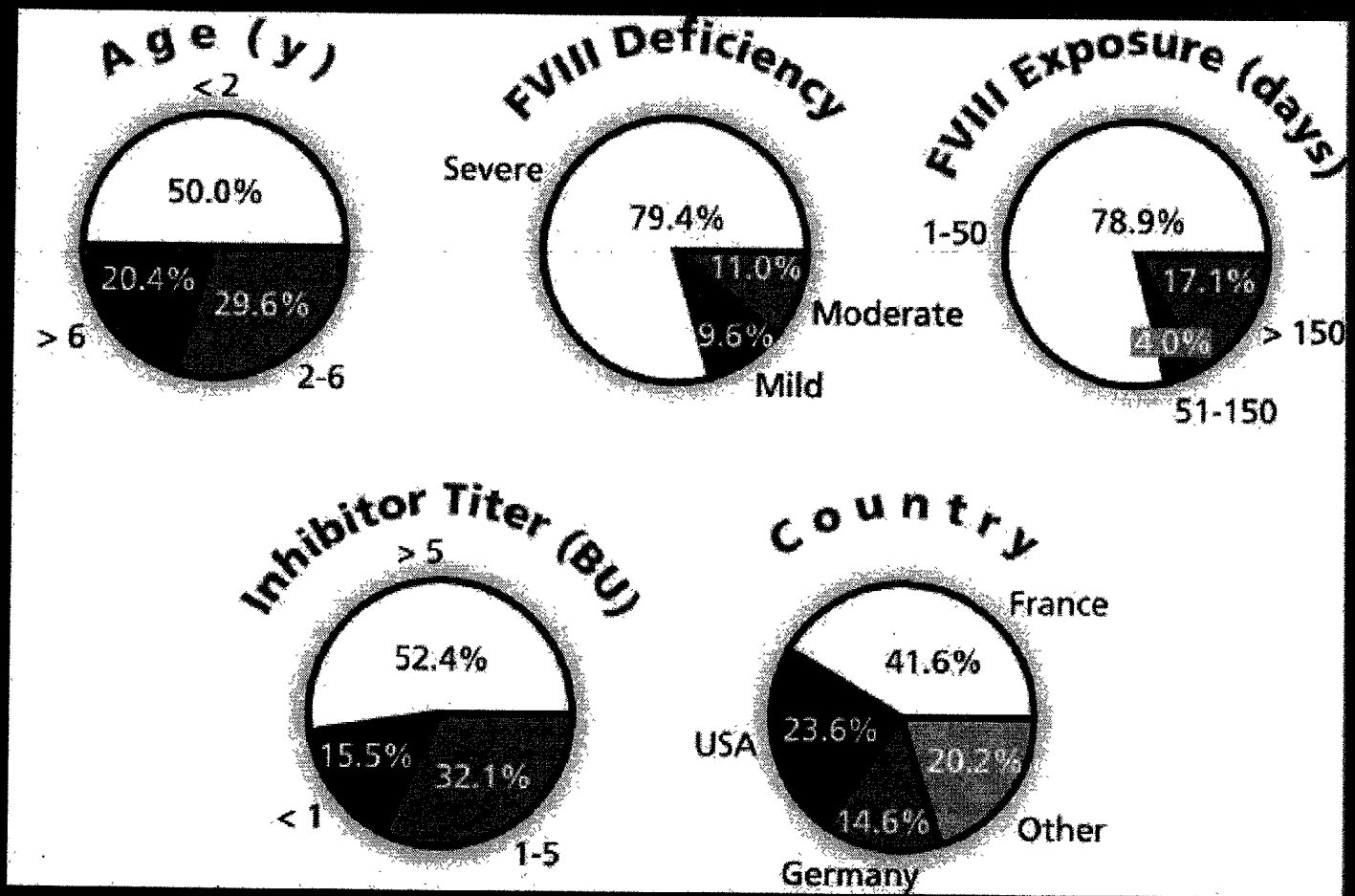
Inhibitor Patient Characteristics



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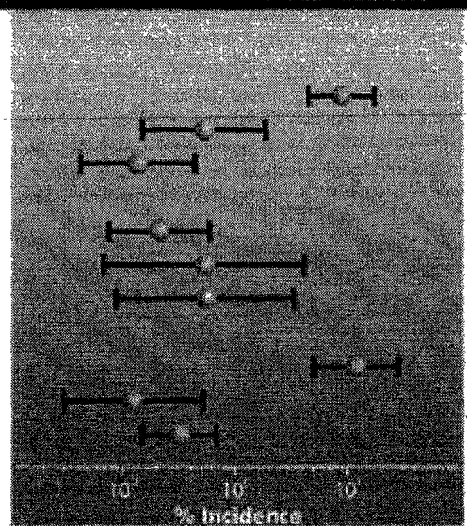
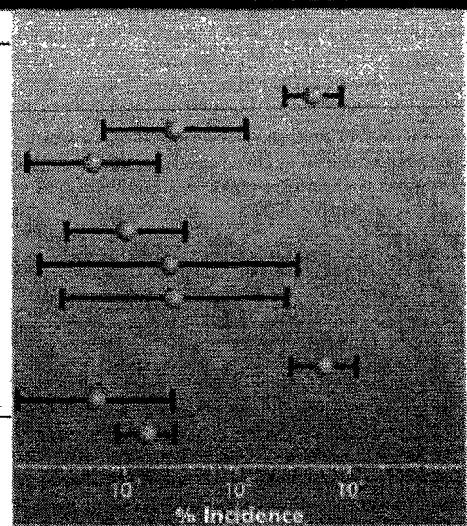
Inhibitor Incidence

Category	All Inhibitors		> 5 BU Inhibitors	
		% Incidence (CI)		% Incidence (CI)
Age (y)				
< 2		8.86 (4.54-17.3)		4.87 (2.70-8.77)
2-6		0.526 (0.149-1.85)		0.285 (0.066-1.23)
> 6		0.135 (0.042-0.436)		0.0530 (0.0139-0.203)
FVIII Deficiency				
Mild		0.210 (0.076-0.581)		0.105 (0.031-0.357)
Moderate		0.531 (0.068-4.14)		0.254 (0.018-3.57)
Severe		0.546 (0.088-3.40)		0.277 (0.028-2.77)
FVIII Exposure (days)				
1-50		11.9 (5.05-28.0)		5.96 (3.00-11.8)
> 50		0.123 (0.030-0.512)		0.0554 (0.0113-0.271)
Total		0.317 (0.149-0.677)		0.158 (0.086-0.286)





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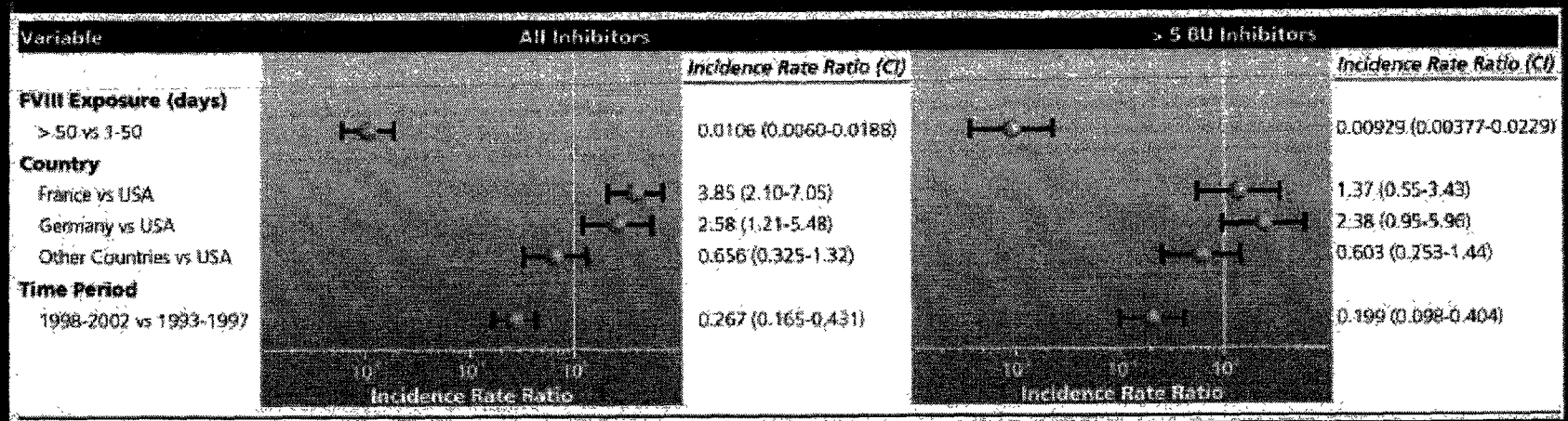
Predictors of Inhibitors



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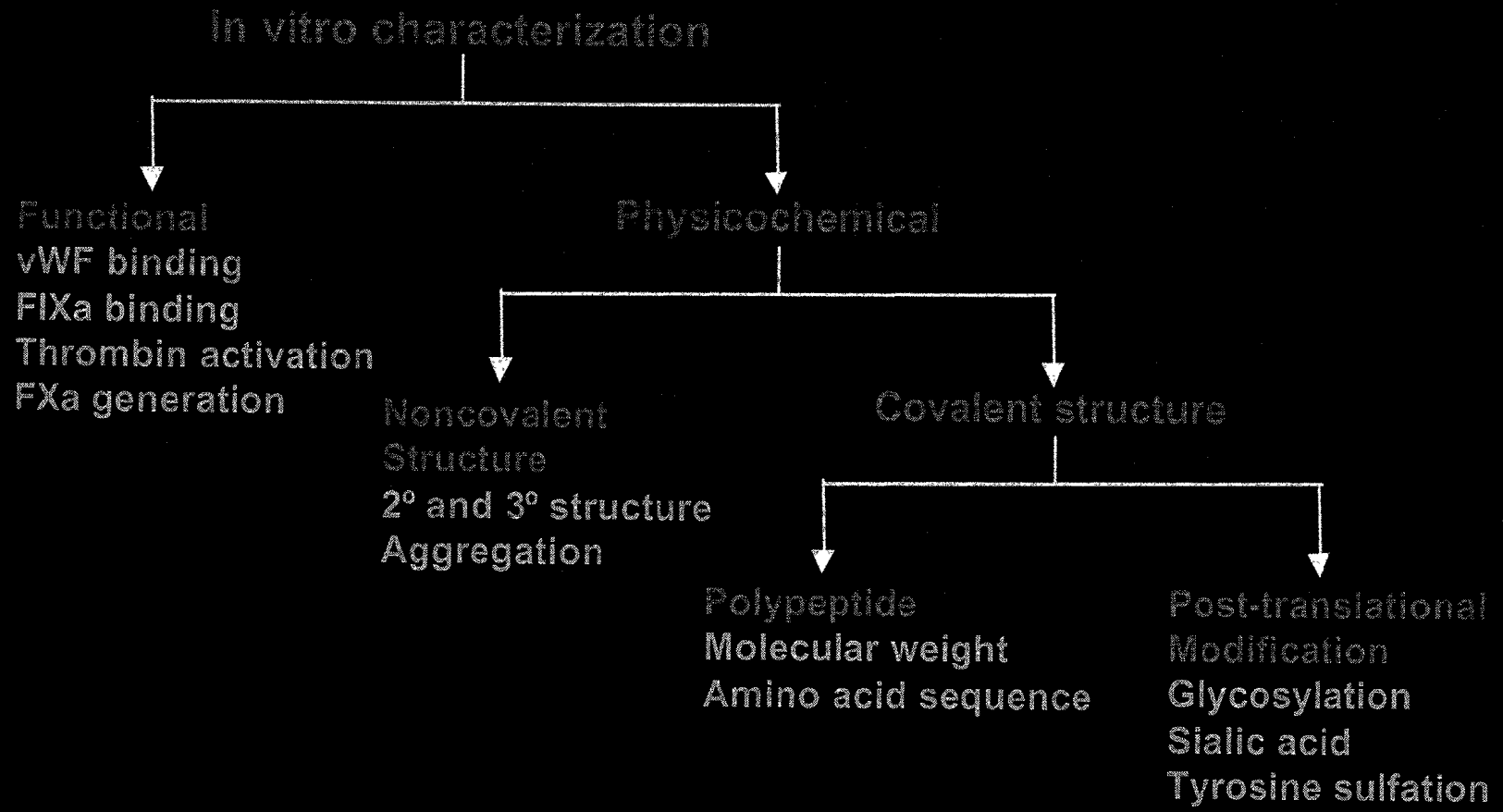
ADVATE rAHF-PFM Preclinical Structural and Functional Analyses



Data on file. Baxter Healthcare Corporation. Mitterer et al. Submitted for publication.

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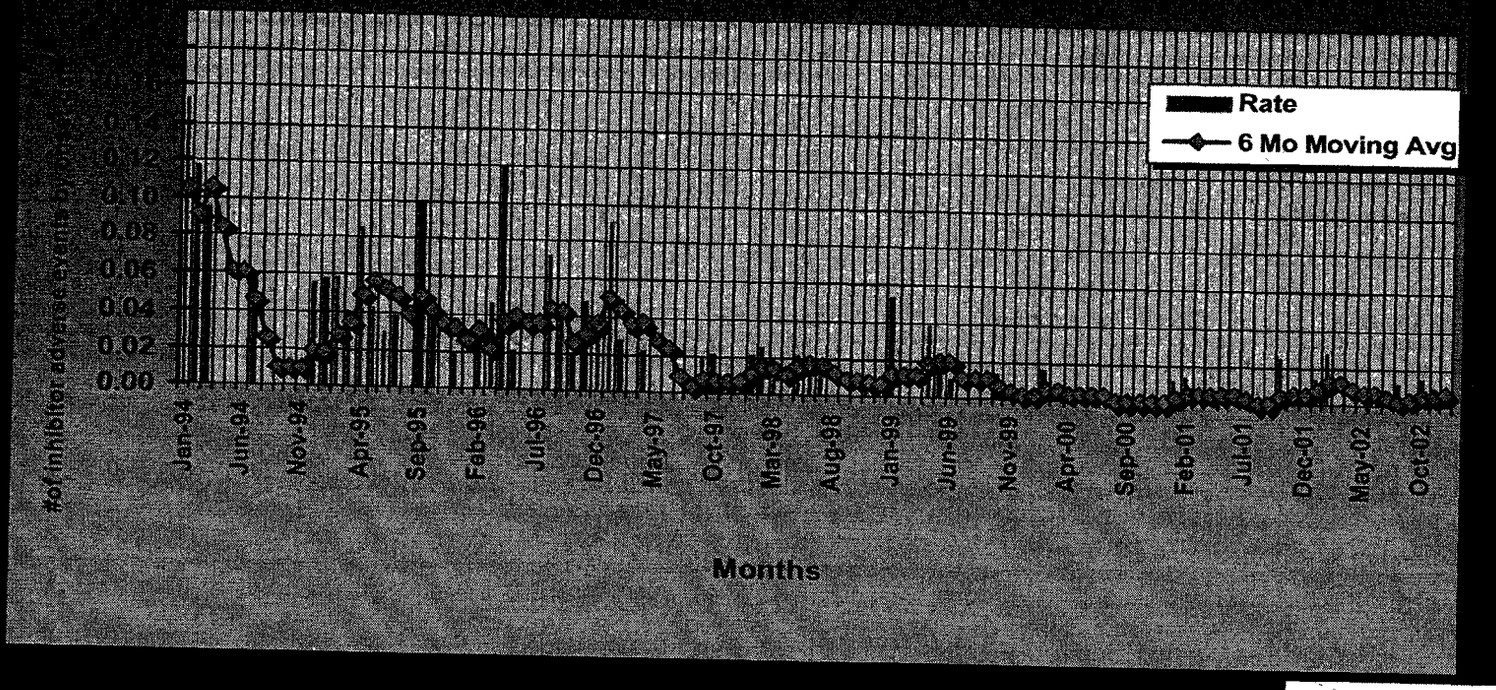
RECOMBINATE & BIOCLATE
INHIBITOR RATE PER MILLION IU SOLD



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Immunogenicity Studies in Animals

- Establishment of FVIII knock-out mice colony
- Injection of hemophilic mice with different formulations of FVIII concentrates
- Measurements of immune responses
  - Total IgG
  - IgG1, IgG2a, IgG2b, IgG3
  - FVIII recovery
- Results found significant differences in anti-FVIII immune responses in hemophilic mice receiving products with major processing differences

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RECOMBINATE
Transient Inhibitors in PUP

Pt. #	Max Inh (BU)	Cum. ED at detection	Inh. duration (mo)	New ED/ mo	Follow up period (mo)	# neg. tests
1	3	8	5	1	53	16
2	0.6	23	3	0.33	31	8
3	0.6	36	8	0.6	12	3
4	1	43	4	2.3	13	5
5	1	10	7	1.1	29	6

- Patients treated with on-demand therapy (20-60 IU/kg) after inhibitor detection
- On-demand therapy continued after inhibitor disappearance free of any anamnestic response

Rothschild et al, Thromb Haemost 2000; 84: 145-6

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